Title

Online only Supplemental Material for: “Cardiovascular Event Prediction by Machine Learning: The Multi-Ethnic Study of Atherosclerosis”

eMethods

Assessment of predictors

Information regarding examinations within MESA has been described previously.[1] Questionnaires were used to ascertain each participant's demographic, smoking status, alcohol consumption, medical conditions, access to medical care, family history of CVD, and use of medications. Physical activity was measured by using a questionnaire adapted from the Cross-Cultural Activity Participation Study. During the examination, anthropometric quantities were measured. Resting blood pressure was measured three times in the seated position using a sphygmomanometer and the average of the last two measurements were used in analysis. Chest computed tomography (CT) performed using either multidetector row CT or electron beam CT measured Agatston score, a well-established measure of coronary artery calcium score (CAC) to evaluate the CAC score per patient.[2] Cardiac magnetic resonance imaging (MRI) was performed using scanners with 1·5-T magnets, and with phased-array surface coils and electrocardiogram gating. Imaging consisted of cine images of the whole heart for size and function assessment of the left atrium[3, 4] and ventricle,[5, 6] phase contrast flow images of measure aortic structure[7] and stiffness[8] and tagged MRI of the left ventricle for regional deformation assessment.[9, 10] For carotid ultrasonography, images of the right and left common and internal carotid arteries were captured, using high-resolution B-mode ultrasound, and the bulb and distensibility of the distal common carotid artery were obtained.[11] To obtain the ankle-brachial index, blood pressure was measured with a Doppler probe in the bilateral brachial, dorsalis pedis, and posterior tibial arteries.[12] For electrocardiography, three 12-lead recordings were obtained using a Marquette MAC-PC instrument, Minnesota coding was used to classify abnormalities.[13-19] Blood was drawn from participants, and aliquots prepared for central analysis. Measurements were performed to assess lipids and lipoproteins,[20] systemic inflammation and hemostasis,[21] N-terminal pro–B-type natriuretic peptide and cardiac troponin-T,[22] and fibrinolysis,[23, 24] and insulin resistance.[25] A random urine sample was collected, with one aliquot being analyzed centrally for creatinine. Online Table I provides a list of the variables used.

Event Adjudication

Events adjudicated as incident heart failure (HF), atrial fibrillation (AF), Dementia, coronary heart disease (CHD), all cardiovascular disease (CVD) and death (or all-cause mortality) as part of the MESA study were used as end-points. In addition to MESA follow-up examinations every two years, a telephone interviewer contacted each participant (or representative) every six–nine months to inquire about all interim hospital admissions, cardiovascular outpatient diagnoses, and deaths. Two physicians reviewed all records for independent end-point classification and assignment of event dates.

Criteria for CHD included any of – myocardial infarction (MI), resuscitated cardiac arrest (RCA), definite angina, probable angina (if followed by revascularization) and CHD death. Reviewers classified MI as definite, probable, or absent, based primarily on combinations of symptoms, ECG, and cardiac biomarker levels. In most cases, definite or probable MI required either abnormal cardiac biomarkers (two times upper limits of normal) regardless of pain or ECG findings; evolving Q waves regardless of pain or biomarker findings; or a combination of chest pain, and ST-T evolution or new LBBB, and biomarker levels one-two times upper limits of normal. Reviewers classified RCA when a patient successfully recovered from a full cardiac arrest through cardiopulmonary resuscitation (including cardioversion). Definite or probable angina required symptoms of typical chest pain or atypical symptoms. Probable angina required, in addition to symptoms, a physician diagnosis of angina and medical treatment for it. Definite angina required one or more additional criteria, including CABG surgery or other revascularization procedure; 70% or greater obstruction on coronary angiography; or evidence of ischemia by stress tests or by resting ECG. Coronary revascularization or, a physician diagnosis of angina, or CHD, in the absence of symptoms, was not considered to be angina. Fatal CHD was classified as definite, possible, or absent. Definite fatal CHD required a documented MI within the previous 28 days, chest pain within the 72 hours before death, or a history of CHD, and required the absence of a known non-atherosclerotic or non-cardiac cause of death. If the definite fatal CHD criteria were not met, possible fatal CHD could be assigned with an underlying cause of death consistent with fatal CHD and required the absence of a known non-atherosclerotic or non-cardiac cause of death.

CVD was considered a composite of MI, RCA, definite or probable angina, stroke, stroke death, CHD death, atherosclerotic death and CVD death. Stroke was classified as present or absent and consisted of rapid onset of a documented focal neurologic deficit lasting 24 hours or until death, or if < 24 hours, there was a clinically relevant lesion on brain imaging. Patients with focal neurologic deficits secondary to brain trauma, tumor, infection, or other non-

vascular cause were excluded. Cause of death was assigned for potential CVD deaths through committee review as part of MESA.

Reviewers classified HF as definite, probable, or absent. Definite or probable HF required heart failure symptoms, such as shortness of breath or edema, as asymptomatic disease is not a MESA endpoint. In addition to symptoms, probable HF required HF diagnosed by a physician and patient receiving medical treatment for HF. Definite HF required one or more other criteria, such as pulmonary edema/congestion by chest X-ray; dilated ventricle or poor LV function by echocardiography or ventriculography; or evidence of left ventricular diastolic dysfunction. We considered participants not meeting any criteria, including just a physician diagnosis of HF without any other evidence, as having no HF.

AF cases were detected using hospital discharge International Classification of Diseases, Ninth Revision (ICD9) diagnosis codes for AF or atrial flutter (427·31 or 427·32). MESA ascertained hospital discharge ICD-9 codes and Centers for Medicare and Medicaid Services (CMS) inpatient hospital claims. AF events during a hospital stay with coronary artery bypass surgery or valve replacement surgery were not counted as incident events.

Death was based on all-cause mortality while an additional endpoint – event-free survival was also examined. Event-free survival was classified as all participants with none of the seven outcomes examined during the follow-up period.

Statistical Analysis

Figure 1 shows the statistical analysis procedures followed in this study. Following data imputation, sufficient data for all predictors and endpoints was available in 6814 participants leading to a total of 5,199,082 data points to predict six outcomes over 10·3 median years of follow-up. As a training data set, 66·6% of the dataset was randomly selected from the overall group of participants; the remaining 33·3% were used as the validation dataset. The training dataset was used for model construction using the different approaches and optimized to reduce prediction error and maximize prediction ability. These models were then tested on the testing dataset to examine model performance and identify the best predictors. Data assembly was performed with STATA version 13·1 (Texas, USA). Analyses were performed using R software (www.r-project.org), using publically available libraries for Cox proportional hazards model (PHM),[26, 27] Lasso-Cox,[28-30] AIC-Cox,[31, 32] and RF methods.[33, 34] The adaptive tree imputation method[35] was used for imputation of missing data.

Survival Random Forest

A binary tree is a decision tool that uses a binary tree-like graph or model of decisions and their possible consequences. It is a flowchart like structure where each node represents a decision (based on a selected variable) and the two branches of the node represent the outcome of the test. Each branch could lead to two leaf nodes and to further subtrees based on the classification. It is one of the most popular techniques used in data mining or machine learning.

The survival random forests (RSF) method, introduced by Ishwaran et al,[33] is an ensemble tree method for analysis of right-censored data. A high-level description of the algorithm can be stated as: (a) drawing bootstrap samples from the data, with each bootstrap sample excluding one-third of the data called out-of-bag data. This is similar to k-fold cross-validation to limit over-fitting; (b) growing a binary survival tree for each bootstrap sample by recursive splitting of tree nodes starting at the root node, which is the top of the tree comprising all data; (c) At each node of the tree including the root node, a subset of all the variables in the dataset are randomly selected - this allows each variable to assert its' importance to event prediction; (d) each node is then split based on the candidate variable (from the subset) that maximizes the survival difference between daughter nodes – this gives us the maximum cumulative hazard function at that node; (e) the tree is grown to full size such that each terminal node, that is the most extreme nodes in a fully grown tree, has at least one unique outcome – this is both an efficient and sufficient stopping criterion; (f) calculating a cumulative hazard rate function for each terminal node within a tree - all cases within the node in a tree will therefore have the same cumulative hazard rate; (g) averaging over all trees to obtain an ensemble hazard function; and (h) using the out-of-bag sample to obtain an out-of-bag prediction error. An illustration is provided in Online Figure I.

While RSF can be used instead of Cox regression analysis for prediction, it can also be used as an efficient variable selection technique either on its own or in conjunction with other methods. For variable selection using RSF, the variables are ranked by the mean of the minimal depth of the maximal subtree over the entire forest. A subtree using a particular variable is defined as a maximal subtree (of that variable) if there is no other subtree (of the full tree) closer to the root node using the variable of interest. The minimal depth of a node is defined as the distance of the node from the root node.

In general, variables appearing higher on the tree, closer to the root node, have a higher rank (and hence are more important) as compared to the variables that appear first near the terminal nodes.

Data transformations, indexing, and imputation
While transformation of variables is not necessary for the RF method, it is necessary for other regression methods to work efficiently. Therefore, we used logarithm transformation for variables as necessary based on the visual histogram (NT pro-BNP, TNF α SR, Troponin-T, C-reactive protein, interleukin-6, homocysteine, aortic distensibility, pulse wave velocity, and Agatston's calcium score). In addition, to allow for easier interpretation (in keeping with prior literature), certain MRI variables were indexed to body surface area – LV mass, volumes, aortic dimensions, and left atrial volumes.

The adaptive tree imputation method introduced by Ishwaran et al was used for imputation of missing data. This algorithm works by adaptively imputing missing data even as the tree is grown by drawing randomly from the set of non-missing in-bag data within the working node. At the end the of the imputation stage, each missing value is replaced by the corresponding average imputed values (or the majority vote for categorical variable) from the entire forest. For the other models, such as the AIC-Cox, LASSO-Cox and Cox PHM models, the imputed dataset with all the missing values replaced using the random forest imputation procedure detailed above was used. All variables available in less than 40% of the population were excluded from analysis. Online Figure II shows the numbers available distribution.

Models tested
We tested eight different models in our analysis in addition to the null model (all regression coefficients = zero). The first model used the random survival forest (RF) algorithm on all available variables.[35] The RF method is an ensemble tree method for analysis of right-censored data. Using the training dataset, 1000 binary survival trees were grown to form an ensemble RF with each tree built on a randomly selected bootstrap sample, which, on average, excluded 37% of the data. From the bootstrap sample, each tree is grown by recursive binary splitting of data, among a subset of 28 randomly selected variables (out of the 735 total). Each split is made by determining a split point of a single variable that maximizes the cumulative hazard of the two resulting data subset, i.e., the daughter nodes. The splitting stops when the data at hand can no longer be split, i.e., reaching the terminal nodes. For each tree, the cumulative hazard rate of a case is determined based on the terminal node that contains it. An ensemble hazard function (and the survival probability) is then estimated by averaging over all trees. The AIC-Cox using the Akaike Information Criterion (AIC) for Cox regression with backward stepwise elimination as well as the LASSO-Cox, a method for variable selection and shrinkage in Cox's proportional hazards model, were also tested in addition to the Cox-PHM.

While RF can be used instead of Cox regression analysis for risk prediction, it can also be used as an efficient variable selection technique either on its own or in conjunction with other methods. For variable selection using RF, the variables were ranked by the mean of the minimal depth of the maximal subtree (highest point in the tree of a variable) over the entire forest (averaged over all 1000 trees). In general, variables appearing higher on the tree, closer to the root node, had a higher rank. The top-20 ranked variables were then used again with RF, AIC-Cox, LASSO-Cox and regularized Cox PHM models.

Performance Evaluation
We assessed the performance of each prediction model to discriminate outcomes at different event times using Harrell's concordance index (C-index),[36-38] and the accuracy of the predictions (mean squared distance between the predicted and actual probabilities) using the Brier score (BS).[39, 40] Performance measures (C-index and BS) for nested models (of the overall models) using subsets of all the predictors (added based on increasing variable importance) were also calculated to assess problems of overfitting. We also compared the results of RF techniques to other known risk scores.[41-43]

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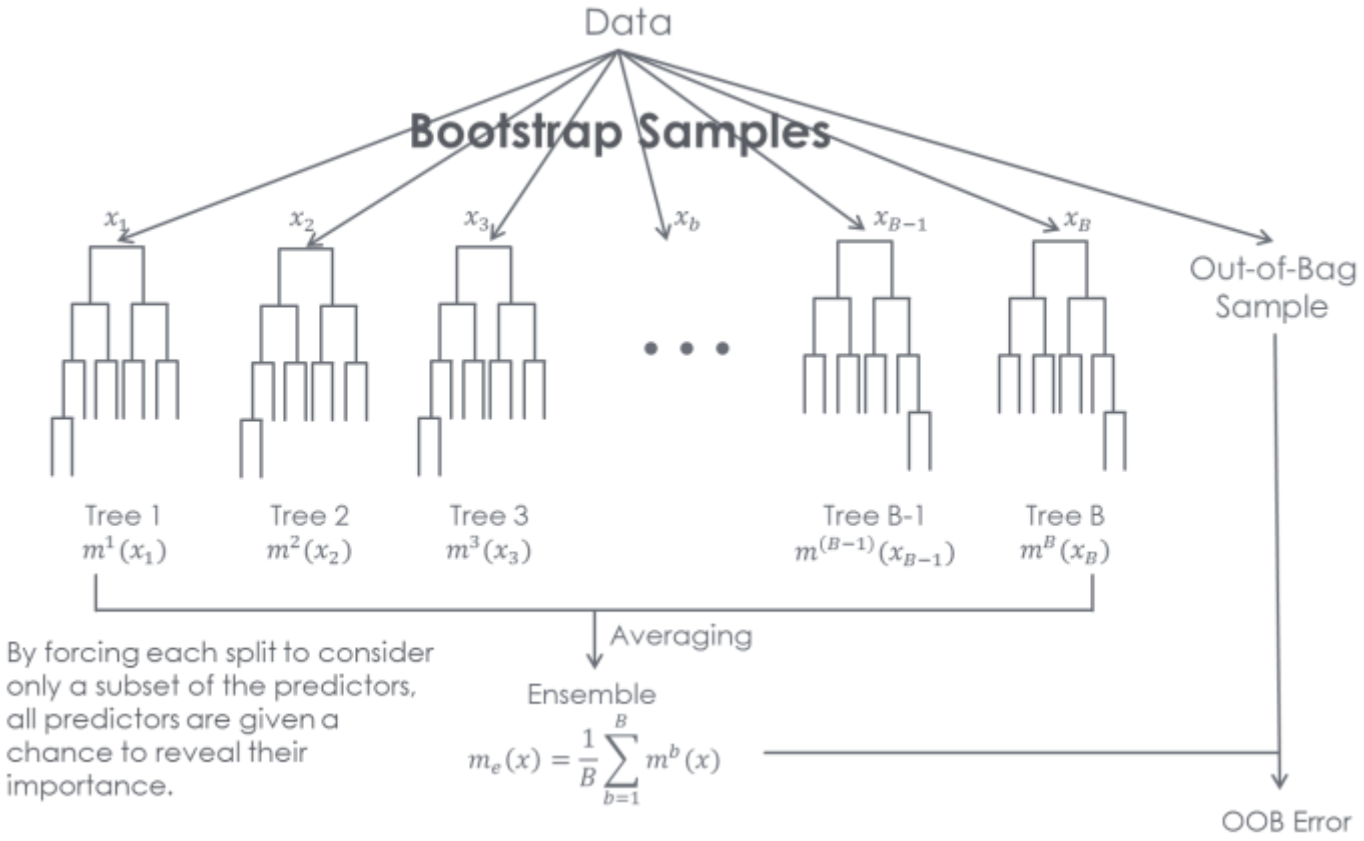
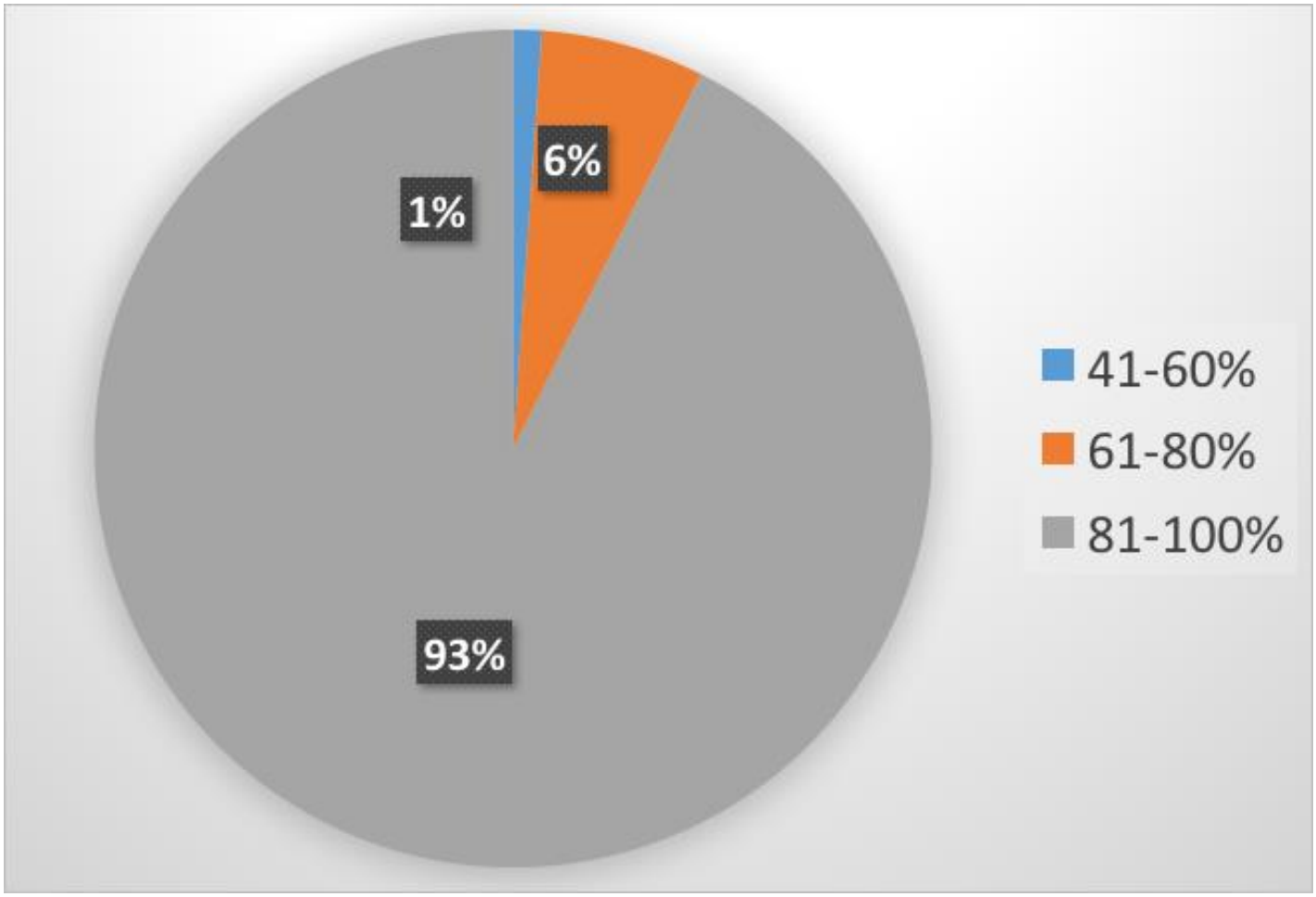
Online Figures and Tables

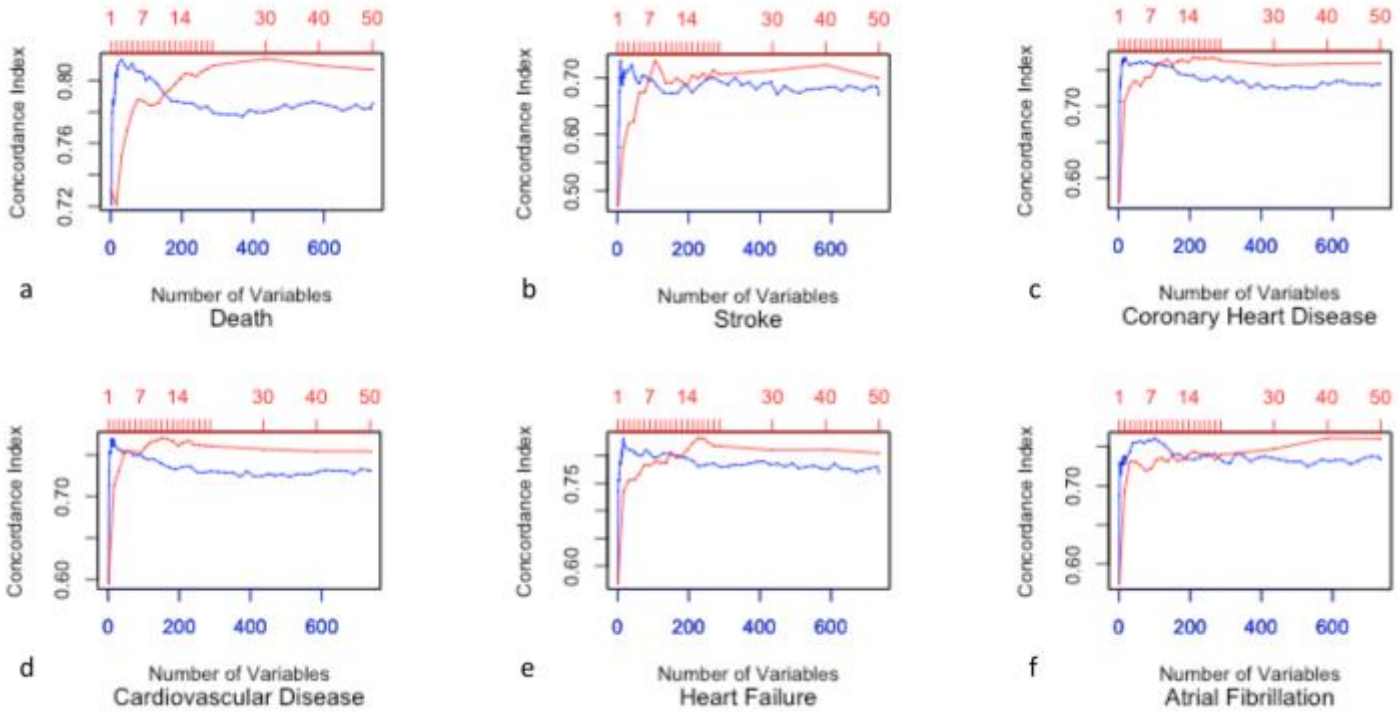
Online Figure I. An illustration of the random survival forest built from a collection of trees.



Online Figure II. The pie chart shows the distribution of available data. The legends indicate the number of participants the variables were available in. The pie chart shows that 93% of the variables were available in over 80% of the population, while only 1% of the variables were available in less than 20% of the population. In all, only 1% of the variables considered were excluded from the analysis.



Online Figure III. Nested RF models showing the change in concordance index with the addition of each of the 735 variables (in blue) by order of increasing rank (variable importance). The red curve indicates the same but only for the top-50 ranked variables on a magnified scale.



Online Table I: The top-10 ranked variables by the variable importance from the random survival forest method for each of the outcomes of interest. The variable importance of each variable was assessed here using permutation testing.

	CHF	CVDA	CHDA	AF	DTH	STRK
1	NT pro BNP	calcium score	calcium score	NT pro BNP	Age	Interleukin-2 soluble receptor
2	LV end-systolic volume	NT pro BNP	TNf a soluble receptor	Age	TNf a soluble receptor	calcium score
3	cardiac troponin T	Interleukin-2 soluble receptor	NT pro BNP	Interleukin-2 soluble receptor	Interleukin-2 soluble receptor	systolic blood pressure
4	TNf a soluble receptor	TNf a soluble receptor	Interleukin-2 soluble receptor	TNf a soluble receptor	NT pro BNP	LV anteroseptal basal end-diastolic wall thickness
5	calcium score	cardiac troponin T	cardiac troponin T	calcium score	calcium score	pulse pressure
6	Age	Age	ABI	creatinine	common carotid IMT	Fasting glucose
7	QT Index	internal carotid CMT	internal carotid CMT	STJ Amplitude in Lead V5 (uV)	ABI	Maximum carotid stenosis
8	LV end-diastolic volume	pulse pressure	maximum ascending aortic area	common carotid IMT	LV anteroseptal basal end-diastolic wall thickness	LV inferior basal end-diastolic wall thickness
9	QTC INTERVAL (msec)	maximum ascending aortic area	Age	internal carotid CMT	LV mass-volume ratio	LV mass-volume ratio
10	Interleukin-2 soluble receptor	ABI	maximum descending aortic area	homocysteine	internal carotid CMT	end-diastolic wall thickness (odbsc1)

Online Table II: The top-10 ranked variables by the variable importance from the random survival forest method for each of the outcomes of interest. The variable importance of each variable was assessed here using the change in Gini Index.

	CHF	**CVDA**	**CHDA**	**AF**	**DTH**	**STRK**
1	LV end-systolic volume	calcium score	calcium score	NT pro BNP	Age	Interleukin-2 soluble receptor
2	NT-pro BNP	NT pro BNP	TNf a soluble receptor	Age	TNf a soluble receptor	T Wave Area (T + T'), Lead AVF
3	Calcium score	TNf-a soluble receptor	ABI	calcium score	Interleukin-2 soluble receptor	Fasting glucose
4	TNf-a soluble receptor	Interleukin-2 soluble receptor	NT pro BNP	creatinine	NT pro BNP	Maximum carotid stenosis
5	LV end-diastolic volume	internal carotid intima media thickness	common carotid intima media thickness	Interleukin-2 soluble receptor	calcium score	internal carotid CMT
6	cardiac troponin-T	cardiac troponin T	cardiac troponin T	common carotid IMT	ABI	R Amplitude in Lead V2 (uV)
7	QTC INTERVAL (msec)	Age	internal carotid intima media thickness	TNf a soluble receptor	common carotid IMT	LV cardiac output
8	LV Ejection fraction	common carotid IMT	LV septal mid-ventricular end-systolic wall thickness	STJ Amplitude in Lead V5	homocysteine	P Wave Area, Lead V2
9	QT Index	maximum ascending aortic area	LV septal basal end-diastolic wall thickness (odbsc1)	ABI	internal carotid intima media thickness	Total QRS Area, Lead V1
10	Interleukin-2 soluble receptor	ABI	Interleukin-2 soluble receptor	R Amplitude in Lead V4 (uV)	maximum ascending aortic area	systolic blood pressure